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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
Y1004/20017

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on _____

Signature _____

Typed or printed name _____

Application Number	Filed
09/826,463	April 5, 2001

First Named Inventor
Nobuto YAMAMOTO

Art Unit	Examiner
1647	David S. ROMEO

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☒ attorney or agent of record.
Registration number 58,313

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

Joseph F. Murphy
Signature

Joseph F. Murphy
Typed or printed name

215-567-2010
Telephone number

August 29, 2006
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 4 forms are submitted.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

Applicant: Nobuto YAMAMOTO

Serial No: 09/826,463 Group Art Unit: 1647

Filed: April 5, 2001 Examiner: ROMEO, D.S.

Att. Docket No.: Y1004/20017 Confirmation No.: 2419

For: PREPARATION OF POTENT MACROPHAGE ACTIVATING FACTORS DERIVED FROM CLONED VITAMIN D BINDING PROTEIN AND ITS DOMAIN AND THEIR THERAPEUTIC USAGE FOR CANCER, HIV-INFECTION AND OSTEOPETROSIS

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action dated May 1, 2006, favorable reconsideration is respectfully requested. A Notice of Appeal in compliance with 37 CFR 41.31 is filed concurrently herewith. Claims 22 and 24 are pending.

REMARKS/ARGUMENTS

Claim 24 is rejected under 35 USC 112, ¶1 as allegedly containing new matter. This rejection is respectfully traversed for the reasons of record set forth in the responses filed 02/17/2006, 07/11/2005, and the reasons set forth below.

In the 7/11/2005 Amendment, claim 24 was amended to recite the limitation wherein "(c) sequencing the cloned Gc1 peptide, thereby confirming that the cloned Gc1 protein is a cloned wild type Gc1 protein". The Examiner argues that the original specification does not describe or suggest the concept of the sequencing procedure in claim 24, step (c). However, the Specification as filed discloses that Applicant was able to determine, using chemically and proteolytically fragmented Gc, that the smallest domain, domain III contains an essential peptide for macrophage activation (page 10, lines 5-7). Furthermore, the Haddad reference (Haddad et al. 1992), which was cited in that paragraph, teaches that it was known in the art to sequence peptides of native serum Gc protein.

The Examiner argues that the Specification only refers to Haddad in regard to vitamin D and actin binding domains of the Gc protein, and that it only refers to chemically and proteolytically fragmented serum (or native) Gc protein. The Examiner further cites portions of Haddad which are seemingly most relevant for construing peptide sequences and argues that this reference only discloses determining the amino-terminal sequence of proteolytic fragments of the Gc protein. The Examiner further argues that the Gc protein sequenced in Haddad, was isolated from its native source and not recombinantly produced. Th Examiner has also newly cited a product datasheet from Calbiochem. Applicant submits that the relevant portion of Haddad which teaches sequencing of the Gc peptide (also known as DBP) is on p. 7175, column 2, ¶2:

> For peptides correlating with radioactivity in paired gel lanes, their stained membrane bands were isolated with a razor blade and were analyzed for amino-terminal sequence in an Applied Biosystems 473A protein sequencer. **The results obtained were compared with the known sequence of hDBP** (Cooke & David, 1985). [Emphasis added].

Thus Haddad, incorporated entirely into the instant Specification, teaches the sequencing of Gc peptide (DBP) and comparison to known, wild-type (hDBP) protein. The limitation in claim 24 subsection (c) is directed to sequencing of the Gc protein to determine whether it is wild-type. This is exactly what Haddad teaches. The fact that the protein source in Haddad is natural versus recombinant as in the present application is irrelevant. Haddad teaches sequencing a Gc peptide and comparing it to wild-type, which is what the limitation covers. The Examiner has further argued that the reference only teaches sequencing of a fragment of hDBP. However, chemically (e.g., cyanogen bromide) and proteolytically (e.g., thrombin) fragmented Gcl protein yields overlapping peptides. Sequencing these peptides allows sequencing full-length Gcl protein. These are the standard and well-established procedures for sequencing full-length proteins. Then, Applicant compares the full-length sequenced data of the cloned Gcl protein with the sequence of the full-length protein, as shown in Fig. 3, with known (or native known) Gcl peptide sequence (Cooke & David. J Clin Invest, 1985; 76:2420-24; also see Yamamoto '002). The claim encompasses sequencing by fragments. This limitation is thus not new matter.

The Examiner has improperly made the May 1, 2006 Office Action final as it is a first action after the Filing of an RCE. On May 1, 2006, the Examiner cited the Calbiochem article as a new piece of art to support the rejection under 35 USC 112, ¶1. The rejection could not have been maintained on the grounds and art of record. Applicant has not been able to respond. While an applicant's cited art can be used to make the action final, here, the Examiner has cited a reference not cited by Applicant. At the least, the finality of the action of May 1, 2006 should be withdrawn.

Reliance on the Calbiochem article is misplaced. Pure hDBP was isolated (Haddad et al.) or purchased from Calbiochem. One should never use Calbiochem Gc protein for peptide sequence studies. Calbiochem Gc protein is a mixed type (see catalog number 385802) which is a mixture of Gc1 and Gc2 because Calbiochem isolated from a mixture of a number of refused blood samples from the Red Cross Blood Bank. The peptide sequence of Gc2 is not identical to that of Gc1.

Accordingly, reconsideration and withdrawal of the rejection of claim 24 under 35 USC 112 first paragraph is respectfully requested.

Claim 22 is rejected under 35 USC 103(a) over U.S. Patent No. 5,177,002 (Yamamoto) in view of Cooke (1985), Quirk (1989), U.S. Patent No. 5,652,352 (Lichenstein), U.S. Patent No. 5,516,657 (Murphy), and Luckow (1995). This rejection is respectfully traversed for the reasons below and of record in the responses filed 02/17/2006, and 07/11/2005.

To establish a prima facie case of obviousness: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; there must be a reasonable expectation of success; and (3) the prior art reference (or combination) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d

1438 (Fed. Cir. 1991), MPEP 2143. To establish prima facie obviousness, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). MPEP 2143.03. Here, the Examiner has not established a prima facie case of obviousness because the combined references do not teach or suggest all the limitations.

The claim covers a process for producing a cloned macrophage activating factor (GcMAFc) by cloning a Gcl isoform into a baculovirus vector, expressing the cloned Gcl isoform, and contacting the cloned Gcl protein with immobilized beta-galactosidase and sialidase, thus obtaining the cloned macrophage activating factor (GcMAFc). In the '002 patent, Applicant purified native Gc isoform from human blood (plasma) and treated it with immobilized β-galactosidase and sialidase to generate GcMAF. This is in contrast to the claimed method. The method disclosed in the '002 patent only generates GcMAF, not GcMAFc as instantly claimed. The '002 patent does not teach or suggest cloning of Gc1, cloning Gc1 in baculovirus vector, or contacting cloned Gc1 with immobilized b-galactosidase and sialidase. The protein disclosed in the '002 patent was not produced by cloning, but by affinity chromatography. This is an important distinction from the instantly claimed method because the native sequence of the Gc1 protein is critical because when cDNA of the major Gc isoform (Gcl) is submitted to baculovirus expression system, protein synthesis occasionally yields mutant Gc peptides having amino acid substitutions due to mistakes made during gene transcription and translation. However, Applicant does not use the cloned mutant peptides to produce GcMAFc because the mutant peptides are immunogenic in humans. Thus, only the cloned Gcl protein having the wild type peptide sequence (Fig 3 of the instant application) should be used to generate GcMAFc. Thus, the cloned Gc protein has to be sequenced, and have the sequence as shown in Figure 3. Only methods of producing the wild type Gcl peptide synthesized via cloning can produce the GcMAFc, as in the instant methods. Treatment of only the cloned Gc protein with immobilized β-galactosidase and sialidase can generate GcMAFc. These deficiencies are not cured by Cooke.

The Examiner relies on Cooke to teach or suggest that the Gc1 allele can be cloned. However, Cooke does not teach or suggest recombinant expression methods. The Examiner, has cited Cooke (1985) for cloning Gc protein via E. coli. However, Cooke only cloned cDNA for Gc1 protein and sequenced the cloned cDNA. The amino acid sequence of the entire Gcl protein was deduced from the cloned cDNA sequence (Figs. 2 ,3 of Cooke). Cooke never expressed Gc protein via the E. coli system, Thus, Cooke never made the amino acid sequence from the protein. Also Cooke never studied the biological activity of the cloned Gc protein because they did not have it: "the primary amino acid sequence of DBP was deduced only after DBP cDNAs were cloned and sequenced." (Cooke at 2422, legend to Figure 3, which shows the predicted amino acid sequence of hDBP). Since the Cooke reference teaches the use of prokaryotic vector mediated cloning, any expressed protein would not be glycosylated. This Gc protein has never been used in *in vivo* biological studies. Thus the combination of the '002 patent and the Cooke reference does not teach or suggest expression of a cloned protein, cloning Gc1 in baculovirus vector, or contacting cloned Gc1 with immobilized b-galactosidase and sialidase. These deficiencies are not cured by the '352 patent.

The Examiner cites the '352 patent as allegedly showing or suggesting expression of Gc protein in insect cells. However, the '352 patent discloses that human afamin, an albumin like protein, can be expressed in insect cells, not Gc1. The albumin protein family consists of four serum proteins, albumin, α-fetoprotein, afamin, and vitamin D-binding protein (Gc protein). They all have three structurally similar

domains. The molecular weight of three proteins (i.e., albumin, α-fetoprotein, and afamin) are approximately 87 kDa whereas Gc protein has smaller molecular weight of 52 kDa. This is because Domain III of Gc protein has a large deletion (equivalent to only 43% of domain III of other albumin family proteins) and thereby the O-glycosylating site (420 threonine residue of Domain III) of the Gc peptide is available for glycosylation. Applicant teaches that Gc protein is the only O-glycosylated albumin family protein. Gc protein is a membrane-like protein as to O-glycosylation, but is as soluble as a serum protein. O-glycosylation usually occurs in membrane proteins and not in serum proteins. The O-glycosylation of protein increases solubility and stability of the cloned protein. Since Gc protein is very different from other albumin family proteins, given the important differences, there is no teaching or suggestion in the '352 patent of the expression and isolation of any and all albumin like proteins, and no teaching or suggestion regarding the specific expression and isolation of Gc1 protein in particular. Thus, the combination of the '002 patent, the Cooke reference, and the '352 patent does not teach or suggest expression of a cloned Gc1 protein, cloning Gc1 in baculovirus vector, or contacting cloned Gc1 with immobilized β-galactosidase and sialidase. These deficiencies are not cured by the Quirk reference.

While the Quirk reference is directed to producing human serum albumin, it is silent on Gc protein. Quirk et al. cloned and expressed human serum albumin in yeast. Although albumin and Gc protein are in the same family of serum proteins, albumin is a non-glycosylated protein, and differs from Gc1, as set forth above. Thus the combination of the '002 patent, the Cooke reference, the '352 patent, and the Quirk reference does not teach or suggest expression of a cloned Gc1 protein, cloning Gc1 in baculovirus vector, or contacting cloned Gc1 with immobilized β-galactosidase and sialidase. These deficiencies are not cured by the '657 Murphy patent and the Luckow reference.

With regard to the recombinant expression of Gc1 in baculovirus, the Examiner relies on the '657 Murphy patent and the Luckow reference, and cites the supposed advantage of baculovirus in the expression of recombinant proteins. However, the only protein that Murphy expressed with this method is the HIV glycoprotein gp120. Unlike the Gc protein, gp120 is not sialylated. There is no evidence in Murphy to suggest that a sialylated protein could be generated as easily due to the nature of protein. The Examiner does not show how or where Luckow teaches or suggests that a baculovirus vector could be successfully employed to express Gc protein in insect cells.

Accordingly, reconsideration and withdrawal of the rejection of claim 22 under 35 USC 103(a) is respectfully requested.

Claims 22 and 24 stand rejected under 35 USC 103(a) over U.S. Patent No. 5, 177,002 (Yamamoto) in view of Cooke (1985), Quirk (1989), U.S. Patent No. 5,652,352 (Lichenstein), U.S. Patent No. 5,516,657 (Murphy), and Luckow (1995), and further in view of Lu (1993). This rejection is respectfully traversed for the reasons below and those of record filed 02/17/2006 and 07/11/2005.

The claims are drawn to a process for producing a cloned macrophage activating factor (GcMAFc) by cloning a Gcl isoform into a baculovirus vector, expressing the cloned Gcl isoform, contacting the cloned Gcl protein with immobilized beta-galactosidase and sialidase, thus obtaining the cloned macrophage activating factor (GcMAFc), and further wherein the cloned protein is sequenced. The base references U.S. Patent No. 5, 177,002 (Yamamoto), Cooke (1985), Quirk (1989), U.S. Patent No. 5,652,352 (Lichenstein), U.S. Patent No. 5,516,657 (Murphy), and Luckow (1995) have been discussed, *supra*. The combination of the '002 patent, the Cooke reference, the '352 patent, the Quirk reference, the '657 Murphy patent, and the Luckow reference does not teach or suggest expression of a cloned Gc1

protein, cloning Gc1 in baculovirus vector, or contacting cloned Gc1 with immobilized b-galactosidase and sialidase, and claim 24 is further drawn to sequence the cloned Gc1 protein, which is also not taught or suggested in these references. These deficiencies are not cured by the Lu reference.

The Lu reference teaches that in order to insure high product quality and to evaluate the effectiveness of manufacturing process in removing contaminants and impurities, a series of analytical methods is required to carry out extensive biochemical characterizations and biological analyses of the final purified product (Lu at 465, column 2, first paragraph). However, the Lu reference is silent with regard to cloning Gc1 in baculovirus vector, contacting cloned Gc1 with immobilized β-galactosidase and sialidase, or sequencing Gc1 protein expressed in insect cells. Since all the limitations of the claims are not taught or suggested by the references, the rejection under 35 USC 103(a) is improper.

Accordingly, reconsideration and withdrawal of the rejection of claims 22 and 24 under 35 USC 103(a) is respectfully requested.

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

August 29, 2006

By _____
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Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.